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Case Report

Nephrology Dialysis Transplantation

Pegylated interferon for the treatment of hepatitis C virus in haemodialysis patients

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Introduction

In patients undergoing maintenance haemodialysis, hepatitis C virus (HCV) infection is common and may lead to severe complications such as chronic hepatitis, cirrhosis and hepatocellular carcinoma. It is recommended to eradicate HCV infection in dialysis patients awaiting renal transplantation and those with acute hepatitis C or significant chronic liver disease. Interferon-α-2a in monotherapy thrice weekly, which is the standard treatment for HCV infection in this setting, has many drawbacks such as poor tolerance and marginal response [1]. The addition of ribavirin is generally contra-indicated in these patients due to a risk of haemolytic anaemia. Pegylated interferon was developed by attaching a large polyethylene glycol (PEG) moiety (40 kDa) to interferon in order to confer greater stability and prolonged systemic exposure to allow once-weekly administration [2]. In two randomized controlled trials, PEG–interferon-α-2a in monotherapy was more efficient than conventional interferon for the treatment of HCV infection associated with chronic liver disease [3,4]. Currently, there is no published experience concerning the use of this compound in patients with end-stage renal disease (ESRD).

Cases

Between January 2002 and April 2003, two HCV patients with biopsy-proven chronic liver disease and one patient with acute hepatitis C were treated with PEG–interferon-α-2a in our institution. Clinical characteristics were as follows.

Case 1

Patient 1 was a 37-year-old male patient known for ESRD due to chronic interstitial nephritis and dialysed since 1992. HCV infection was diagnosed in 1996, following routine screening. A renal transplantation was performed in 1997 but dialysis was resumed in 2000 because of chronic allograft rejection. He was then considered for a second renal transplantation. A pre-transplant evaluation revealed persistent elevation of liver enzymes and positivity for antibodies to HCV. The HCV genotype was 1b. The HCV RNA level was 290 kIU/ml. A liver biopsy showed moderately active hepatitis and fibrosis (Metavir score A2F2).

Case 2

Patient 2 was a 61-year-old man on dialysis for ESRD secondary to vascular and hypertensive nephropathy. He received a cadaveric renal allograft in 1987 and was found to be positive for anti-HCV antibodies in 1991, presumably consecutive to graft transmission. Chronic hepatitis C progressively developed, and liver cirrhosis Child A was diagnosed in 2000. Dialysis consequently was resumed and the transplant removed in 2002. A double kidney–liver transplantation was considered. A liver biopsy confirmed moderate micronodular cirrhosis (Metavir score F4). Liver enzymes were normal and HCV RNA level was 253 kIU/ml. Typing revealed HCV genotype 3a.

Case 3

Patient 3 was a 56-year-old man who had been undergoing haemodialysis since 2001 because of ESRD due to autosomal dominant polycystic kidney

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disease. In January 2002, he suddenly developed nausea, vomiting, diarrhoea, fatigue and frank elevation of liver enzymes. Acute hepatitis C was diagnosed. Although the cause of HCV infection was not clearly identified, exposure to infected material from the haemodialysis setting was thought to be the most likely source. The HCV RNA level in serum was 594 kIU/ml and HCV genotype was 1b.

Treatment

Each patient was scheduled to receive subcutaneous treatment with PEG–interferon-α-2a (Pegasys®, Roche, Basle, Switzerland) over 48 weeks, starting at 180 μg once weekly, immediately following the dialysis session. Patients were monitored by weekly blood formulae and a precise dose-adjustment schedule according to blood cell count; patient clinical tolerance was applied according to the manufacturer's recommendations (Table 1). During the treatment period, the patients underwent three dialysis sessions of 3 h 30 min per week through high-flux polysulfone dialysers.

The HCV RNA level was determined in serum by polymerase chain reaction (PCR) assay (Cobas Amplicor HCV Monitor assay, Roche Diagnostics Systems) immediately before the haemodialysis session. Samples were collected at the following time points: 1–4 weeks before the treatment was started, during the treatment at weeks 12, 24 and 48, and 6 months after the end of the treatment, i.e. at week 72. The absence of detectable levels of HCV RNA was defined as <50 IU/ml. Sustained virological response (SVR) was defined as the absence of detectable levels of HCV RNA in serum at 72 weeks, i.e. 6 months after the end of treatment. Genotype analysis was carried out by reverse transcriptase–PCR followed by hybridization of amplified products on an array of genotype-specific probes [Versant® HCV genotype assay (LiPA), Bayer].

Table 1. Treatment schedule and monitoring of side effects

Parameter	Downward dose adjustment of PEG–interferon
Neutrophil count (cell/mm^3)	
>1000	None
750–999	Weeks 1–2: immediate one level adjustment Weeks 3–48: no adjustment
500–749	Weeks 1–2: delay or hold dose until >750, then resume dose with one level adjustment Weeks 3–48: Immediate one level adjustment
250–499	Weeks 1–2: Delay or hold dose until >750, then resume dose with two level adjustment Week 3–48: Delay or hold dose until >750, then resume dose with one level adjustment
<250	Stop drug
Platelet count (cell/mm^3)	
>50 000	None
35 000–49 000	Delay or hold dose until >50 000, then resume dose with one level adjustment
25 000–34 000	Delay or hold dose until >50 000, then resume dose with two level adjustment
<25 000	Stop drug

Pegasys® (40 kDa branched PEG–interferon-α-2a) dose adjustments for low absolute neutrophil and platelet counts: assigned dose, Pegasys® 180 μg; one level adjustment, Pegasys® 135 μg; two level adjustment, Pegasys® 90 μg; three level adjustment, Pegasys® 45 μg.

The applied treatment and clinical follow-up of the patients are summarized in Table 2. HCV RNA was undetectable in all three patients after 12 weeks of therapy. In patients 1 and 3 (genotype 1b), HCV RNA remained undetectable during the entire 48 week treatment course and these patients reached SVR. In contrast, the viraemia reappeared under treatment at 24 weeks in patient 2 (genotype 3a) without elevation of liver enzymes. This situation was considered as a failure of therapy and Pegasys® treatment was stopped.

Most of the observed side effects such as anorexia, weight loss, insomnia, depression and flu-like symptoms were predictable and manageable. Myelotoxicity was mitigated by strict adherence to the dose-reduction schedule, so that neutropoenia and thrombopoenia remained moderate and not associated with clinically related events. Anaemia needed an increase of recombinant epoetin doses, enabling haemoglobin levels to be maintained without blood transfusions. Two adverse events were peculiar and deserve a special description. Patient 2 complained of chronic dry cough associated with bilateral interstitial infiltrates on chest X-ray. Both cough and lung infiltrates disappeared when dry weight was decreased and recurred 4 months after Pegasys® therapy was stopped. Extensive investigations revealed mixed interstitial and obstructive bronchopneumopathy. Oral steroids allowed resolution of symptoms, but minimal lung infiltrates persisted. A side effect of Pegasys® treatment could not be ruled out. Patient 3 presented cutaneous bullous lesions on both hands, diagnosed as pseudoporphyria cutanea, after 8 months of Pegasys® treatment. Furosemide, a frequent cause of dialysis-related pseudoporphyria cutanea, was stopped and the lesions progressively disappeared within 3–4 months. Thus, whether this side effect was attributable to Pegasys® or not remains unclear.

Discussion

Conventional interferon in monotherapy leads to SVR rates of 30–40% in patients on dialysis [1]. However, a high percentage of adverse events and early discontinuations makes this treatment difficult to apply in these patients. PEG–interferon-α-2a and 2b have significantly improved antiviral therapy for HCV in patients without renal insufficiency [3,4]. Furthermore, PEG–interferon-α-2a is more efficient than standard interferon-α-2a in HCV patients with genotype 1 [3]. This report is the first to describe the use of pegylated interferon in haemodialysed patients. PEG-interferon-α-2a was chosen since this compound is mostly cleared via hepatic metabolism, in contrast to PEG-interferon-α-2b, which essentially shows renal clearance.

Table 2. Treatment, responses and side-effects

	Patient 1	Patient 2	Patient 3
Liver disease	Chronic hepatitis	Cirrhosis Child A	Acute hepatitis
HCV genotype	1b	3a	1b
Effective treatment duration	48 weeks	24 weeks	48 weeks
Weekly dose and causes of dose adjustments	180 μg for 48 weeks	180 μg for 4 weeks Decrease to 90 μg for 2 weeks (thrombopoenia, insomnia) Increase to 135 μg for 10 weeks Decrease to 90 μg for 8 weeks (thrombopoenia)	180 μg for 7 weeks Decrease to 135 μg for 4 weeks (neutropoenia) Decrease to 90 μg for 37 weeks (neutropoenia and depression)
HCV RNA level at 72 weeks (SVR)	Not detectable	189 kIU/ml at 24 weeks	Not detectable
ALAT	Normalized at 12 weeks	Normal (entire follow-up)	Normalized at 4 weeks
Minimal Hb level (g/l)	103	92	125
Minimal leukocyte count (G/L)	2.8	2.8	1.3
Minimal neutrophil count (G/L)	1.0	1.4	0.5
Minimal platelet count (G/L)	107	49	107
Side effects	None	Weight loss, insomnia (oxazepam prescription), cough and X-ray infiltrates	Weight loss, fatigue, depression (citalopram prescription) flu-like symptoms, cutaneous bullous lesions

G/L = giga/liter

Furthermore, its pharmacokinetics following a single dose subcutaneous administration are already known in patients with ESRD [5]. In the latter study, different pharmacokinetic parameters were assessed using ascending doses of Pegasys®. The dose of 180 μg led to the highest area under the curve, but serum half-life and maximal concentrations of the drug were similar to those seen in healthy subjects [5]. Thus, we elected to initiate the treatment at this dose, being prepared to reduce it according to weekly clinical and haematological observations.

In patients without renal insufficiency, acute hepatitis C can be treated successfully in 24 weeks [6]. However, the natural history of HCV acute infection in dialysed patients is less predictable and usually less favourable [7,8]. In the absence of guidelines in this particular setting, we felt that a treatment of 48 weeks in patient 3 might have given the best chance to eradicate the virus in order to make the patient eligible to receive a renal transplant.

SVR was observed in both HCV patients with genotype 1b, which is a remarkable finding since this genotype is typically associated with lower success rates. There was no serious adverse event and the reported side effects were manageable by appropriate dose reductions.

Conclusion

In this cumulative experience of 30 months, PEG–interferon-α-2a appears to be an interesting treatment option in HCV patients undergoing maintenance haemodialysis. Large controlled studies are now needed to confirm these encouraging preliminary data.

Conflict of interest statement. None declared.

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